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ORIGINAL ARTICLE

Neuroimaging adolescents with depression in a middle-income country: feasibility of an fMRI protocol and preliminary results

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Abstract

Objective: To test the feasibility and to present preliminary results of a neuroimaging protocol to evaluate adolescent depression in a middle-income setting.
Methods: We assessed psychotropic medication-free adolescents (age range 14-16 years) with a diagnosis of major depressive disorder (MDD). Participants underwent a comprehensive clinical evaluation and both structural and functional magnetic resonance imaging (fMRI). In this pilot study, a preliminary single-group analysis of resting-state fMRI (rs-fMRI) data was performed, with a focus on the default mode network (DMN), cognitive control network (CCN), and salience network (SN).
Results: The sample included 29 adolescents with MDD (mean age 16.01, SD 0.78) who completed the protocol. Only two participants were excluded due to MRI quality issues (head movement), and were not included in the analyses. The scans showed significant connectivity between the medial prefrontal cortex and posterior cingulate cortex (DMN), the ACC and anterior insula (SN), and the lateral prefrontal cortex and dorsal parietal cortex (CCN).
Conclusion: We demonstrated the feasibility of implementing a complex neuroimaging protocol in a middle-income country. Further, our preliminary rs-fMRI data revealed patterns of resting-

state connectivity consistent with prior research performed in adolescents from high-income countries.

Keywords: Depression; adolescent; neuroimaging

Introduction

Major depressive disorder (MDD) in youth is a highly prevalent and comorbid condition, and a leading cause of disease burden[1] with a high rate of recurrence.[2] Furthermore, adolescence is a period of heightened neuroplasticity, encompassing profound developmental changes with important alterations to both the structure and function of the brain.[5] In addition, adolescence is a time of increased emergence of many psychiatric conditions, including depression.

In an attempt to better elucidate the neural underpinnings of depression in youth, research has focused on the neurobiological correlates of the disorder.[6] The integration of clinical phenomenology and neurobiology aims for a better understanding of mental disorders and their impact on affected individuals. While we are yet to translate most neuroimaging research findings into clinical practice, there is a large body of evidence to support the interplay between neural circuits and clinical depression.[7] Among the most widely used neuroimaging techniques to observe such effects, resting-state functional magnetic resonance imaging (rs-fMRI) has been linked to favorable results in terms of reproducibility and consistency across studies.[8] Three of the major circuits frequently evaluated in rs-fMRI studies of individuals with depression, defined as sets of brain regions that display correlated activity during rest,[9] are the default mode network (DMN), the salience network (SN), and the cognitive control network (CCN).

The DMN is activated during moments of passive rest and suppressed during goal-directed tasks.[10] The network is most notably comprised of the medial prefrontal cortex (MPFC) and the posterior cingulate cortex (PCC), and has been consistently shown to exhibit aberrantly increased connectivity in individuals with depression when compared with healthy controls.[11] The SN is associated with environmental detection of salient changes,[12] and its major nodes include the dorsal anterior cingulate cortex (dACC) and anterior insula (AI). The CCN is implicated in higher order cognitive functions, and is constituted by the dorsolateral prefrontal cortex (DLPFC), the ACC, and the dorsal parietal cortex (DPC).[13] Hypoconnectivity within and between the SN and CCN networks has been evidenced in individuals with depression.[14]

Much of the global burden of youth depression comes from its effects on populations of low- and middle-income countries (LMICs), where most of the world's youth population lives.[1,15,16] Nevertheless, the majority of research in depression has been conducted in high income countries (HICs),[17] a phenomenon that came to be known as the 10-90 divide – only 10% of the randomized clinical trials for mental health conditions affecting youth were performed in LMICs, where 90% of the child and adolescent population live.[16] The same disparity is observed in the field of brain imaging. A recent bibliometric review found that among the 100 most highly cited neuroimaging studies in psychiatric disorders, only six had a LMIC researcher as first author[18] (China in all cases). In Brazil, only one large neuroimaging study designed to assess various outcomes in terms of psychopathology with published data on youth depression is available.[19] Considering that depression has been inversely associated with socioeconomic status and educational levels in both high-income[3] and low- and middle-income settings,[4] differences in the rs-fMRI connectivity patterns observed in patients with MDD in LIMCs vs. HICs might be expected. Understanding clinical and neurobiological characteristics of depression among children and adolescents living in LMICs is crucial for the overall understanding of the global burden of youth depression, and comparing neuroimaging findings across populations from HICs

and LMICs may provide unique insights to enhance our understanding of which biological risk processes are relatively universal across different populations, and which are context-specific.

Focusing on the development and applications of state-of-the-art research methods generally employed in HIC, the Identifying Depression Early in Adolescence (IDEA) consortium is a multinational initiative to improve the early identification of MDD in adolescents.[1] Researchers from Brazil, Nepal, Nigeria, the United Kingdom, and the United States are collaborating to devise strategies for stratifying adolescents at high- and at low-risk for developing depression. In focusing on LMICs for this type of multilevel research, we hope to reduce the existing research disparity. Studying the neurobiology of depression in youth from LMICs may also help to identify effects of physical and emotional deprivation, trauma, humanitarian crises, family history of psychopathology and lower educational levels that may more strongly contribute to MDD's development and recurrence in these contexts.

In this study, we present data showing the feasibility of implementing a complex MRI protocol in a LMIC country. Furthermore, we present the results of a preliminary analysis of rs-fMRI data from 29 psychotropic medication-free adolescents with a current diagnosis of MDD. We structured our findings in three major sections: methodology description (in which we specify selection criteria, the comprehensive clinical evaluation, and the selection of neuroimaging parameters); MRI quality control (describing the steps taken to ensure image quality); and the preliminary results obtained with 29 MDD participants.

Methods

Sample and design

The present pilot is part of a larger study that is currently in the process of data collection, with a projected sample of 105 adolescents who will undergo a full clinical evaluation as well as collection of biomarker and neuroimaging data. The data in this preliminary analysis refer to MDD participants recruited in the initial 6 months of the study. All participants were recruited from a convenience sample of 57 public state schools located near Hospital de Clínicas de Porto Alegre (HCPA), Brazil, where the evaluations are performed. Screening for depressive symptoms was performed using the Patient Health Questionnaire for Adolescents (PHQ-A),[20] with a score of 10 or higher being considered as positive screening for depression. The present analyses refer to 31 participants with MDD; two were excluded due to quality issues (see quality control criteria below), and thus the final analysis included 29 participants.

Phone screening

After the initial screening at the schools, conducted through self-administered questionnaires, participants were contacted over the phone for full screening to confirm eligibility. This phone screening phase was performed by three trained investigators to check participant contact information and to assess inclusion and exclusion criteria. Each adolescent and their primary caregiver were invited for the clinical phase of our study and, upon verbal assent, answered a series of structured questions over the phone. First, we inquired about the presence of any metal implants (i.e., braces, pacemakers, prosthetics, cochlear implants, and mechanical heart valves) or clinical limitations (i.e., pregnancy and claustrophobia) that would contraindicate MRI data collection. Second, to avoid possible confounders to the biomarker or neuroimaging analyses, we inquired about relevant clinical comorbidities (i.e., epilepsy, known brain malformations, and inflammatory disorders) and chronic use of medications (i.e.,

psychotropic, steroidal or non-steroidal anti-inflammatory drugs, and beta-blockers). Adolescents not meeting the exclusion criteria were scheduled for the clinical phase of our study.

Clinical assessment

Following the phone assessment, each adolescent came to the HCPA clinical research center accompanied by a primary caregiver for a comprehensive clinical evaluation performed by a board-certified child and adolescent psychiatrist. After being informed about the procedures, caregivers provided written consent and adolescents provided verbal and written assent to participate in the study. The protocol was approved by both the HCPA ethics committee and the Brazilian National Ethics Committee, (project number 50473015.9.0000.5327).

To assess adolescents for a full range of psychiatric disorders, participants (self-report) and caregivers (parent-report) were independently interviewed by a board-certified child and adolescent psychiatrist using the Brazilian Portuguese version of the Schedule for Affective Disorders and Schizophrenia for School-Age Children-Present and Lifetime Version (K-SADS-PL)[21]. Other measures included the Children's Depression Rating Scale-Revised (CDRS-R),[22] the Children's Global Assessment Scale (CGAS), and the Columbia-Suicide Severity Rating Scale (C-SSRS).[23] Among the self-reported measures were the three versions (adolescent self-report, parent-report on adolescent, and parent-report on own symptoms) of the Mood and Feelings Questionnaire (MFQ).[24] Pubertal status was ascertained by a score of at least 2 in a self-reported Tanner scale.[25] Parents also provided thorough information on family history of mood disorders via a structured interview developed by our research group, covering data on the diagnosis of depression or bipolar disorder, history of past or current psychiatric admissions, and suicide attempts for all first- and second-degree family members; and completed a Brazilian standardized measure of socioeconomic status,[26] which is a widely used set of questions about the ownership of house appliances, access to basic sanitation and street pavement, as well as family provider level of education. This validated measure of socioeconomic status in Brazil generates a score ranging from 0 to 100. Intelligence quotient (IQ) was estimated using the Wechsler Abbreviated Scale of Intelligence (WASI),[27] administered by a trained psychologist. The full list of instruments filled out by adolescents and parents is available as Online-Only Supplementary Material. To confirm the diagnosis of current MDD, clinicians utilized all the available sources of information to generate a case formulation, which was discussed in a clinical committee chaired by a senior child and adolescent psychiatrist (CK). For biomarker analysis, blood and saliva sample were collected, and axillary temperature was measured at the time of blood draw. Full study inclusion and exclusion criteria for each phase are described in Table 1.

Table 1 Criteria for sample composition

Phase	**Inclusion criteria**	**Exclusion criteria**
School interviews	Age 14 to 16 years	Absence from school on the day of the assessment; inability to complete the screening questionnaire
Phone screening	Having completed school questionnaire; right-handedness	- Metallic accessories - Chronic clinical conditions* - Use of psychotropic medication over the last 30 days - Use of anti-inflammatory medication over the last 14

		days
Clinical assessment	Intelligence quotient > 70: post-pubertal status: current major depressive disorder	Current or lifetime: - bipolar disorder - psychotic disorder - autism spectrum disorder - substance use disorder - eating disorder - post-traumatic stress disorder

* Excluded clinical conditions: known brain malformations, epilepsy, recent traumatic brain injury, diabetes, cystic fibrosis, current inflammatory disorders (i.e., asthma, rheumatologic conditions, and oncologic conditions), and severe neurodevelopmental disorders.

Data collection

All clinical data were collected and managed using Research Electronic Data Capture (REDCap) tools[28] hosted at HCPA. REDCap is a secure, web-based application designed to support data capture for research studies, providing: 1) an intuitive interface for validated data entry; 2) audit trails for tracking data manipulation and export procedures; 3) automated export procedures for seamless data downloads to common statistical packages; and 4) procedures for importing data from external sources. All instruments were adapted to a digital version and uploaded to the REDCap database by researchers in our group. Instruments that have conditional branches depending on initial responses by the participants, (e.g., the K-SADS-PL) had their algorithms fully implemented in the REDCap system by our team, via built-in functions such as "branching logic." This facilitated data collection and clinical decision-making, while reducing the possibility of human error in the prompt assessment of structured and semi-structured interviews.

MRI protocol

The last evaluation step, after clinical diagnosis of depression and biomarker collection, was structural and functional MRI acquisition. The ultimate aim of the protocol is to determine differences in brain structure and function in adolescents with MDD vs. those without MDD. For each participant, clinical assessment and MRI were conducted sequentially on the same day.

A whole-brain T1-weighted anatomical scan was collected from every participant. fMRI was performed both in passive rest (resting-state, rs-fMRI) and during a series of tasks. Two different tasks were used to engage both the reward network and the emotion network: the gambling task, adapted and translated into Brazilian Portuguese from Barch et al.[29]; and the emotional face matching task, adapted and translated into Brazilian Portuguese from Hariri et al.[30] Both fMRI tasks use a block design, and block orders were counterbalanced to reduce potential carryover effects. In the present report, we provide initial data for the first 29 participants with MDD adequate neuroimaging data. Structural and task-based fMRI data will be reported once data collection is complete.

Image acquisition

All images were acquired using a 3T Ingenia scanner (Koninklijke Philips N.V., The Netherlands), software version 5.3.1., purchased by HCPA in 2017 in an attempt to expand the

imaging research capacity of the institution. Along with the machine, an Esys fMRI by Invivo with a 32" screen and console system was installed, consisting of two task-dedicated computers, two button boxes, a response control pad, and an MRI-compatible screen with a set of mirrors to be used inside the MRI room. Tasks were run in a dedicated computer using E-prime Runtime version 3.0.

High-resolution structural images were collected using T1 weighted MPRAGE volumetric acquisition in sagittal plane with TR (repetition time) = 8.55 ms, TE (echo time) = 3.94 ms, TI (inversion time) = 900 ms, flip angle = 8º, field of view = 240 × 240 mm, 170 slices with 0.94 mm thickness, acquisition matrix 256 × 256, resulting in a 0.94 × 0.94 × 0.94 mm^3 voxel resolution. Blood oxygenation level dependent signal (BOLD) images were collected with the following acquisition parameters: TR = 2000 ms, TE = 30 ms, flip angle = 90°, in transaxial plane aligned to the anterior and posterior commissure line, field of view = 240 × 240 mm, 36 slices with 3.5 mm thickness, slice gap 0.35 mm, and acquisition matrix 80 × 80. The gambling task was administered in four runs (90 volumes and 3:10 minutes each); the emotional face matching task was administered for one run (277 volumes and 9:24 minutes); and the resting-state functional connectivity (rsFC) scan was administered for 6:52 minutes (206 volumes). During the resting state scan, participants were shown an image of a fixation cross on the screen and were instructed to let their minds wander.

Magnetic resonance imaging (MRI) quality control

MRI system quality is assessed weekly through Philips Imaging Quality Tool (PIQT) as part of the institutional MRI quality control program. It is a pass/fail automatic tool that provides information about the global system performance and individual evaluation for the central frequency (magnetic field drift), spatial linearity, imaging uniformity, spatial resolution, and head coil signal to noise ratio (SNR). SNR showed the highest variation among all parameters. All image quality parameters remained within the values specified by the manufacturer during data collection.

Resting-state functional connectivity (rsFC) pre-processing and quality assurance

The rsFC images were pre-processed in the Conn toolbox (https://web.conn-toolbox.org). Pre-processing steps included realignment and unwarping, slice-timing correction, detection of outlier scans, segmentation and normalization of functional images into a standard stereotaxic space (Montreal Neurological Institute [MNI]), and smoothing with 6 mm full width at the half maximum (FWHM) Gaussian kernel. BOLD images were bandpass filtered to a 0.009Hz-0.08Hz window. In addition, to minimize the influence of head motion on rsFC analyses, volumes were censored according to the conservative criteria within the Conn toolbox (any volumes exceeding a global-signal Z-value threshold of 3 or a 0.5 mm volume-to-volume motion threshold). Participants with more than 10% of volumes censored based on these criteria were excluded; this resulted in the removal of two participants from the data set (both had over 10% of volumes censored due to head motion), leaving a total of 29 participants with data meeting all quality control criteria.

Statistical analyses

Data analyses included a description of the sample characteristics and comparison for sex differences, using *t* tests for quantitative variables and chi-square tests for categorical variables.

For rsFC, seed-to-voxel analysis was used to report connectivity within three networks hypothesized to play a role in depression: the DMN, the SN, and the CCN. Seeds were defined using the Conn toolbox's network-based seeds and included the MPFC (DMN), the dACC (SN), and the right and left LPFC (CCN). RsFC images were generated for each seed and then fed into group-level analyses in the Conn toolbox to test whether each seed was connected with expected regions in its network in the pilot sample. The thresholds used to examine connectivity within each network were $p < 0.001$ for corrected voxelwise and $p < 0.05$ for false discovery rate (FDR)-corrected at the cluster-level. The results for clusters with a minimum size of 100 voxels are reported.

Results

Sample characteristics

The final sample included 29 adolescents with a current diagnosis of MDD, clinical evaluation, and successful MRI acquisition. Sample characteristics are presented in Table 2.

Table 2 Sample characteristics

	Overall	**Male**	**Female**
Age	16.01 (0.78)	16.16 (0.93)	15.93 (0.70)
Sample size, n (%)	29 (100.00)	10 (34.48)	19 (65.52)
Skin color (self-reported), n (%)			
White	16 (55.17)	6 (60.00)	10 (52.63)
Non-white	13 (44.83)	4 (40.00)	9 (47.37)
MFQ-C	41.41 (9.87)	39.89 (8.71)	42.21 (10.56)
MFQ-P	20.66 (11.85)	24.33 (14.21)	18.74 (10.31)
CDRS	53.34 (10.01)	49.91 (10.14)	55.16 (9.72)
Any psychiatric comorbidity, n (%)	19 (65.52)	7 (70.00)	12 (63.16)
WASI (IQ) score	91.48 (9.43)	97.78 (8.36)	88.16 (8.34)*
Socioeconomic status†	35.67 (19.89)	32.22 (8.73)	37.32 (23.48)
Parental history of mood disorder, n (%)‡	19 (65.52)	7 (70.00)	12 (63.16)
MFQ-A	21.90 (14.77)	20.60 (13.49)	22.58 (15.71)

Data presented as mean (standard deviation), unless otherwise specified.
CDRS = Children's Depression Rating Scale; MFQ-A = Mood and Feelings Questionnaire, Adult Version; MFQ-C = Mood and Feelings Questionnaire, Child Version; MFQ-P = Mood and Feelings Questionnaire, Parent Version; WASI = Wechsler Abbreviated Scale of Intelligence.
* $p < 0.05$ for the comparison between males and females.
† Based on Kamakura et al.[26]
‡ Family history of mood disorder was operationalized as history of major depressive disorder, bipolar disorder, or suicide attempt in any parent.

In this sample, 55.17% of the adolescents reported their skin color as white. Regarding socioeconomic status, family income was about 16% higher than the average for the city of Porto Alegre (where the data were collected and the adolescents live), and around 65% higher than the national average income.[31] Mean IQ scores were considered within the average for this age range, while depression symptoms were high, as expected, in both the MFQ-C and CDRS. Further, most participants had parental history of depression, bipolar disorder, or suicide attempt. Finally, about two-thirds of the sample had at least one psychiatric comorbidity, with generalized anxiety disorder and attention deficit hyperactivity disorder (ADHD) being the most frequent (seven and two affected adolescents respectively). When comparing measures between sexes, only WASI scores were statistically different, with boys having a higher mean than girls. The difference in all other measures was not statistically significant for the sex comparison. Interestingly, there was a significant disparity between the MFQ-C (self-report by the adolescents) and the MFQ-P (parent report on youth symptoms) ($p < 0.05$), with adolescent depressive symptoms largely underreported by the parents.

MRI quality control

In order to ascertain the quality of fMRI acquisition, specific items of the EPI acquisition were assessed, as suggested by the American Association of Physicists in Medicine (AAPM) Report 100 from 2010.[32] These performance tests were performed every 6 months, for a total of two data points during the present study (immediately before and after data collection). Among the parameters evaluated, the means were 1.79% for ghosting ratio, 1.29% for geometric distortion, and 0.18% for EPI stability coefficient of variation. The maximum suggested values for such parameters are, respectively, 3, 3, and 0.25%. Our findings were well within the suggested values, which attests to the technical quality of our MRI acquisition.

Resting-state functional connectivity (rsFC)

The findings obtained for all three major networks evaluated (DMN, SN, and CCN) were consistent with the previous literature on HIC. In DMN, there was positive connectivity between the MPFC, the angular gyrus, and the PCC (Figure 1A). The SN exhibited positive connectivity between the ACC and AI (Figure 1B), while the right and left LPFC were positively connected to the DPC in the CCN (Figures 1C and 1D, respectively). See the Online-Only Supplementary Material for statistics and coordinates.

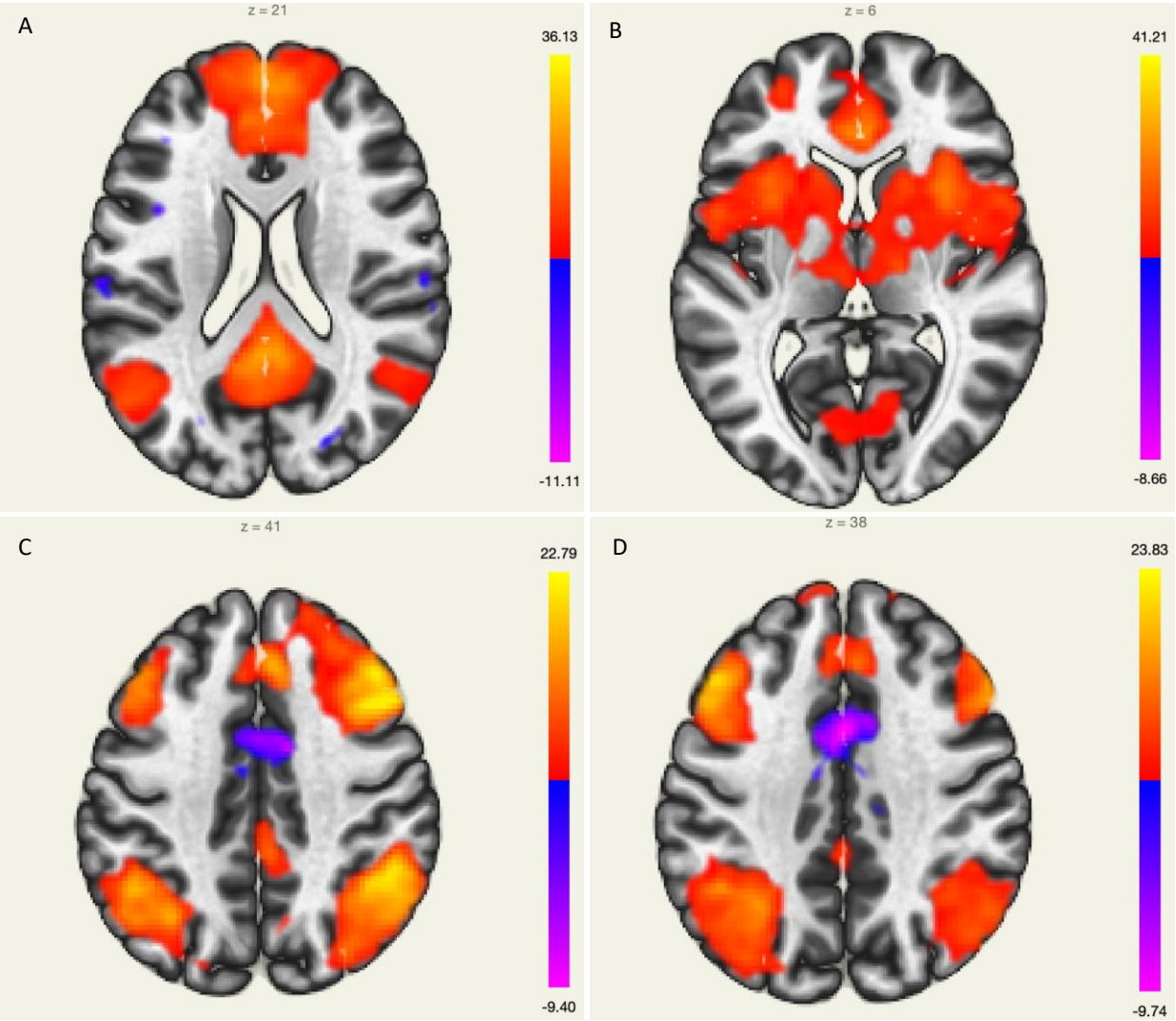

Figure 1 Resting-state functional connectivity (rsFC) in three major networks of a sample of adolescents with major depressive disorder (n = 29). A) Default mode network showing positive connectivity between the medial prefrontal cortex, the angular gyrus, and the posterior cingulate cortex. B) Salience network exhibiting positive connectivity between the anterior cingulate cortex and the anterior insula. C, D) Right and left lateral prefrontal cortex, respectively, highlighting positive connectivity with the dorsal parietal cortex in the cognitive control network.

Challenges and difficulties

Considering that the present results refer to the onset of fMRI studies in our institution, a series of challenges had to be overcome in all steps of data collection. A large number of adolescents had either dental braces or a fixed retainer that is commonly placed behind the lower teeth after the removal of braces, and both are contraindications to undergo MRI in our institution. The presence of metal accessories (especially orthodontic devices) in general accounted for about 30% of exclusions on the phone screening. Further, we had a few issues with the MRI equipment during the protocol: in one case, the screen malfunctioned during MRI

acquisition; the participant was unable not complete the fMRI tasks and had to be excluded. The reason for that was a failure in the screen power supply which had to be replaced. The usual replacement time of 1 month was fortunately reduced to 1 week with support from the institution. During this period, all data collection was interrupted. Aside from that, some minor technical issues (software malfunctions, power outages) had to be handled, but no data were lost.

Discussion

Depression provides an important contribution to the burden of disease in youth worldwide, and these effects might be even more pronounced in LMICs. Neuroimaging research holds the potential for elucidating the neurobiology of depression and revealing the mechanisms of development of risky patterns of brain function. However, there are still relatively few neuroimaging studies addressing this issue. Given the disparity in the volume of research performed in HICs as compared to LMICs, high quality research must be performed in LMICs to better elucidate the particular characteristics of depressed youth in these countries.

Here, our main goal was to describe the development and application of a high-quality neuroimaging protocol that would still be feasible despite the financial and technical barriers expected in a middle-income country. We also performed a preliminary analysis of fMRI data to ensure that data collection and quality control standards would be comparable to those in HICs.

Our final sample in this pilot study consisted of 29 adolescents with depression who underwent a comprehensive clinical evaluation (with several measures of depression and other psychiatric comorbidities), a collection of blood and saliva for future biomarker analysis, and a full MRI protocol involving structural MRI, resting-state and task-based fMRI. Only two participants were excluded for MRI quality issues (head movement), which is comparable to large neuroimaging studies in HIC.[33] Further, our sample is within expected ranges for demographic characteristics in Brazil according to the national census,[34] with both skin color and socioeconomic status closely related to the local population averages. As expected, participants exhibited high levels of depressive symptomatology in all scales. Parents largely underreported adolescent symptoms of depression. While this was somewhat expected given the internalizing nature of MDD,[35] it also reinforces the importance of measuring symptoms directly with the adolescents for diagnosing depression using the available psychometric tools.

Preliminary analyses of rs-fMRI data revealed patterns of resting-state connectivity consistent with prior research in HICs.[10-12] Specifically, we observed the expected patterns of significant connectivity between the MPFC and PCC (DMN), the ACC and AI (SN), and the LPFC and DPC (CCN). These results indicate that we were able to effectively measure rs-fMRI within these networks in a LMIC setting, laying the foundation for future analyses to examine whether connectivity within these networks correlates with indices of risk for depression and depression severity. This will allow us to address important questions regarding which findings from prior research on the neurobiology of depression are relatively universal across different parts of the globe, and which are context-specific.

Our study has limitations that must be addressed. First, as a pilot study, the focus was restricted to the feasibility of data collection and basic group data analyses. The small number of participants might have increased the chance of type II error. Also, we did not, at this point, run more complex correlations between depressive symptoms and MRI findings. Thus, the possibility that rsFC or the other measures varied as a function of depression severity was not assessed at this point, and will be analyzed once full data collection is complete. Further, since we are evaluating a wide range of biomarkers in our sample, there were several exclusion criteria

unrelated to the neuroimaging itself that might have produced bias and reduced external validity. Finally, our sample had slightly higher income than the Porto Alegre average, but showed socioeconomic differences from the overall Brazilian population in terms of ethnicity and income, with a higher percentage of white and lower proportion of non-white teenagers. Brazil is a country with over 34 million adolescents[34] living in a variety of socioeconomic contexts, and further studies will be required to adequately capture all the regional differences.

Among the strengths of our study is the carefully phenotyped, psychotropic drug-free nature of the sample. Also, the present protocol will allow three groups of adolescents to be compared: participants with MDD and those at both low- and at high-risk for developing depression subsequently. Therefore, the present study is among the first to have fMRI data collected and stratified based on depression risk and clinical diagnosis among adolescents in LMICs, which adds to the relevance of the findings. Further, our sample had blood and saliva samples collected for biomarker analysis, adding to the wide array of techniques used to analyze multiple facets of depression. Lastly, all our data (clinical, biomarkers, and neuroimaging) were collected on the same day for each participant. Such a strategy fills an important gap, since most studies collected neuroimaging data several days/weeks after clinical evaluation. Since depressive symptoms usually change over the span of days or weeks, we believe more reliable correlations between the clinical evaluation and neuroimaging will be detected with the present protocol.

Conclusions

This is an important preliminary study that aims to shed light on depression in LMICs, where most affected individuals live. We have shown the feasibility of a complex fMRI protocol all the way from design to data analysis. As one of the first fMRI studies of youth depression in LMIC, we hope these findings will reduce the overall disparity and contribute with quality data on this very important group of individuals.

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Disclosure

LAR has been on the speakers' bureau/advisory board and/or has acted as a consultant for Eli-Lilly, Janssen-Cilag, Medice, Novartis/Sandoz, and Shire/Takeda in the last 3 years; receives authorship royalties from Oxford Press and ArtMed; received travel awards for taking part of 2016 American Academy of Child and Adolescent Psychiatry (AACAP) and 2018 American Psychological Association (APA) meeting from Novartis and Shire. The ADHD and Juvenile Bipolar Disorder Outpatient Programs chaired by him received unrestricted educational and research support from the following pharmaceutical companies in the last 3 years: Eli-Lilly, Janssen-Cilag, Medice, Novartis, and Shire. VM has received research funding from Johnson & Johnson, a pharmaceutical company interested in the development of anti-inflammatory strategies for depression, but the research described in this paper is unrelated to this funding. The other authors report no conflicts of interest.

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